Remarks

Claims 1-35 are pending and under examination in the subject application. Applicants have hereinabove amended the specification to correct a typographical error, replacing the term "carbonsol" with "carbon in a sol". In addition, applicants have hereinabove amended claims 1, 2, 4, and 7-35, and canceled claims 5 and 6. Applicants maintain that the amendments to the claims raise no issue of new matter. Support for the amendments to claim 1 can be found in the specification as originally filed at, *inter alia*, page 12, lines 4-17. Support for the amendments to claim 2 can be found in the specification as originally filed at, *inter alia*, page 13, line 25 to page 14, line 18. Support for the amendments to claim 4 can be found in the specification as originally filed at, *inter alia*, page 14, lines 23-27. Support for the amendments to claim 7 can be found in the specification as originally filed at, *inter alia*, page 16, lines 8-28. Support for the amendments to claim 8 can be found in the specification as originally filed at, *inter alia*, page 16, line 30 to page 17, line 19. Support for the amendments to claim 9 can be found in the specification as originally filed at, *inter alia*, page 16, lines 8-28. Support for the amendments to claim 10 can be found in the specification as originally filed at, *inter alia*, page 18, lines 18-22. Support for the amendments to claim 11 can be found in the specification as originally filed at, *inter alia*, page 17, lines 26-27. Claim 12 has been amended to correct a typographical error that appeared in the application as filed, and which has also been amended hereinabove, and is supported at page 17, line 28. Support for the amendments to claim 13 can be found in the specification as originally filed at, *inter alia*, page 17, lines 23-24. Support for the amendments to claim 14 can be found in the specification as originally filed at, *inter alia*, page 18, lines 1-3. Support for the amendments to claim 15 can be found in the

specification as originally filed at, *inter alia*, page 18, lines 4-5. Support for the amendments to claim 16 can be found in the specification as originally filed at, *inter alia*, page 18, lines 5-6. Support for the amendments to claim 17 can be found in the specification as originally filed at, *inter alia*, page 18, lines 6-7. Support for the amendments to claim 18 can be found in the specification as originally filed at, *inter alia*, page 18, lines 9-10. Support for the amendments to claim 19 can be found in the specification as originally filed at, *inter alia*, page 18, lines 10-14. Support for the amendments to claim 20 can be found in the specification as originally filed at, *inter alia*, page 18, lines 24-29; page 16, lines 8-28; and page 16, line 30 to page 17, line 19. Support for the amendments to claim 21 can be found in the specification as originally filed at, *inter alia*, page 19, lines 9-17, page 16, line 30 to page 17, line 19; page 18, lines 24-29; page 16, lines 8-28; and page 16, line 30 to page 17, line 19. Support for the amendments to claim 22 can be found in the specification as originally filed at, *inter alia*, page 18, lines 24-29, and at page 16, lines 8-28. Support for the amendments to claim 23 can be found in the specification as originally filed at, *inter alia*, page 9, line 12-18. Support for the amendments to claim 24 can be found in the specification as originally filed at, *inter alia*, page 18, line 30 to page 19, line 7. Support for the amendments to claim 25 can be found in the specification as originally filed at, *inter alia*, page 19, line 16. Support for the amendments to claim 26 can be found in the specification as originally filed at, *inter alia*, page 19, line 17. Support for the amendments to claim 27 can be found in the specification as originally filed at, *inter alia*, page 16, lines 8-28; and at page 9, line 26, to page 10, line 1. Support for the amendments to claim 28 can be found in the specification as originally filed at, *inter alia*, page 19, lines 19-26, and page 16, lines 8-28. Support for the amendments to claim 29 can be found in the

specification as originally filed at, *inter alia*, page 19, lines 19-26, and page 16, line 30 to page 17, line 19. Support for the amendments to claim 30 can be found in the specification as originally filed at, *inter alia*, page 19, lines 26-28. Support for the amendments to claim 31 can be found in the specification as originally filed at, *inter alia*, page 20, line 23. Support for the amendments to claim 32 can be found in the specification as originally filed at, *inter alia*, page 20, line 22. Support for the amendments to claim 33 can be found in the specification as originally filed at, *inter alia*, page 20, lines 5-12. Support for the amendments to claim 34 can be found in the specification as originally filed at, *inter alia*, page 19, line 16; and at page 20, line 13. Support for the amendments to claim 35 can be found in the specification as originally filed at, *inter alia*, page 19, line 17; and at page 20, line 14. Accordingly, applicants respectfully request entry of this Amendment. After entry of this Amendment, claims 1-4 and 7-35 will be pending and under examination.

Claims Rejected Under 35 U.S.C. §112 (Second Paragraph)

In the June 30, 2003 Office Action, the Examiner stated that claims 1-35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that in claims 1-35, recitations of "such" or "such type" are vague and indefinite as to what is intended as encompassed. The Examiner stated that it is not clear if previously recited elements are intended or are merely exemplary of the recited "such" elements. The Examiner stated that recitations of "the" or "said are proper for elements having an antecedent basis.

In response, applicants have hereinabove amended the claims to remove the term 'such'.

The Examiner also stated that in claim 1 and claims dependent thereupon, "the presence" lacks antecedent basis. The Examiner further stated that in claim 2 and claims dependent thereupon, "the presence" lacks antecedent basis. The Examiner stated that in these claims it is not clear how to do a comparison of steps (b) and (c) in step (c), it is believed that steps (a) and (b) were intended.

In response, applicants have hereinabove amended the claims to include proper antecedent basis and refer to the appropriate claim steps.

The Examiner stated that in claim 7 and claims dependent thereupon, the interrelationships of the components are not clear, for example it is not clear if the samples comprise affixed ganglioside prior to the contacting step. The Examiner stated that in these claims it is not clear what is being determined if a standard is provided indicative of the amount of antibody in the subject, it is believed that a standard indicative of sample amount was intended. The Examiner stated that in these claims, "the amount" lacks antecedent basis.

The Examiner stated that in claim 8 and claims dependent thereupon, it is not clear what is being determined if a standard is provided indicative of the amount of antibody in the subject, it is believed that a standard indicative of sample amount was intended. The Examiner stated that in these claims, "the amount" lacks antecedent basis.

In response, without conceding the correctness of the Examiner's

position, but in order to expedite prosecution, applicants have hereinabove amended claims 7, 8, and 9 to more clearly claim the subject matter.

The Examiner stated that in claims 10 and 14, improper Markush language is used to claim the members of the group. The Examiner stated that the alternative "selected from...or" or "selected from the group consisting of...and" are acceptable.

In response, applicants have hereinabove amended the claims to recite permitted disjunctive language.

The Examiner stated that in claim 10, it is not clear how a liquid sample can be selected from tissue or lymph nodes as alternatives.

In response, without conceding the correctness of the Examiner's position, but in order to expedite prosecution, applicants have hereinabove amended claim 10 to more clearly claim the subject matter.

The Examiner stated that in claim 16, "the source" lacks antecedent basis.

In response, without conceding the correctness of the Examiner's position, but in order to expedite prosecution, applicants have hereinabove amended claim 16 to more clearly claim the subject matter.

The Examiner stated that in claims 20, 21, 28, 33, and claims dependent thereupon, "using" is not a valid method step. The Examiner stated that in these claims, "the presence" lacks antecedent basis.

In response, applicants have hereinabove amended the claims to correct antecedent basis and to remove invalid method language.

Claims Rejected Under 35 U.S.C. §102(b)

The Examiner stated that claims 1-3, 5, 6, 10, and 14-19 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Uhlig et al. (Autoimmunity 5: 87-99, 1989). The Examiner stated that Uhlig et al. prepared blue-dyed liposomes (see Fig. 2 legend) having mixtures of glycolipids, including gangliosides (e.g. from extracts of human myelin or bovine brain glangliosides), or selected pure lipids thereon (e.g. pages 91-92) and determined the ability of IgM autoantibodies in samples to agglutinate the liposomes as an indication of antigen-autoantibody binding (pages 39-95). The Examiner stated that samples were reacted with a series of microparticle populations having different concentrations of different glycoplipids thereon and presence or absence of agglutination was determined.

In response, applicants respectfully traverse the Examiner's rejection. Specifically, applicants note Uhlig et al. discloses liposomes having mixtures of glycolipids thereon, as stated by the Examiner, but Uhlig et al. do not disclose ganglioside affixed to solid particles as recited in applicants' claimed subject matter. Applicants note that liposomes, as taught by Uhlig et al. are not solid particles but bilayers enclosing an aqueous, i.e. liquid, compartment. In support of this, applicants submit herewith as **Exhibit A**, a copy of pages 220-221 of Biochemistry, J. David Rawn, 1989, ISBN 0-89278-400-8, which in the second paragraph of page 220 states that liposomes are "..bilayers that enclose an aqueous compartment..", and are "vesicle[s]", and illustrates such in Figure 9-16 on page 221.

Furthermore, applicants note that nowhere does Uhlig et al. state a method involving "microparticles", but only discloses using liposomes. Accordingly, applicants maintain that Uhlig et al. do not teach all the elements of applicants' claimed invention, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated that claims 1-3, 5, 6, 8-10, 13, 14, 18 and 19 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Uemura et al. (Biochem. J. 219: 865, 1984). The Examiner stated that Uemura et al. teach that hemagglutination with serial dilutions of sample was known for the detection of autoantibodies which bind gangliosides.

In response, applicants respectfully traverse the Examiner's rejection. Specifically, applicants note Uemura et al. discloses antibodies that can elicit hemagglutination, i.e. agglutination of red blood cells, not solid particles as recited in applicants' claimed subject matter. Accordingly, applicant maintains that Uemura et al. do not teach all the elements of applicants' claimed invention, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §103(a)

The Examiner stated that claims 1-3, 5, 6, 8-10, 13, 14, and 17-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Uemura et al. (Biochem. J. 219: 865, 1984) in view of Ravindranaths et al. (J. Biol. Chem. 263: 2079, 1988). The Examiner stated that the teachings of Uemura et al. are as set forth above and differ from the invention as instantly disclosed in to teaching coating the solid phase, i.e. the erythrocytes, with purified gangliosides in the assay.

The Examiner stated that Ravindranaths et al. teach coating asialo-erythrocytes with gangliosides for hemagglutination assays (e.g. page 2080, col. 2). The Examiner stated that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used the coating method of Ravindranaths et al. with the hemagglutination assay taught in Uemura et al. in order to determine the specificity of the autoantibodies of Uemura et al. because one of ordinary skill in the art would have been motivated to substitute coated erythrocytes in the assay to obviate the need to stock erythrocytes with different antigen types as used in the method taught in Uemura et al. or to obviate the need to perform thin layer chromatography binding assays to determine antibody specificity. The Examiner stated that one would have had a reasonable expectation of the success of the known hemagglutination method for the successful detection of antibody specificity. The Examiner stated that thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

In response, applicants respectfully traverse the Examiner's rejection. Specifically, applicants note Uemura et al. disclose antibodies that can elicit hemagglutination, i.e. agglutination of animal cells, not solid particles as recited in applicants' claimed subject matter, and Ravindranaths et al. do not cure this deficiency. Accordingly, applicants maintain that the rejected claims define an invention not obvious from the cited references, and therefore not properly rejected under 35 U.S.C. 103(a), and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated that claims 1-35 are rejected under 35 U.S.C.

§ 103(a) as being unpatentable over Uhlig et al. (Autoimmunity 5: 87-99, 1989) in view of Dwyer et al., Uemura et al. (Biochem. J. 219 865, 1984), Ravindranaths et al. (J. Biol. Chem. 263 2079, 1988), Pestronk (U.S. Pat. No. 5, 443, 952), and applicants' admissions regarding the prior art.

The Examiner stated that the teachings of Uhlig et al. are as set forth previously and differ from the invention as instantly claimed in not teaching particles other than liposomes for performance of the agglutination assay and in not teaching anti-glycolipid antibodies in peripheral neuropathy patient samples. The Examiner also stated that Dwyer et al. teach coated polystyrene spheres as an alternative to liposomes for agglutination assays using particle surface-exposed gangliosides. The Examiner stated that as set forth above, Uemura et al. teach that hemagglutination was known for the detection of autoantibodies which bind gangliosides. The Examiner stated that further Ravindranaths et al. teach coating asialo-erythrocytes with gangliosides for hemagglutination assays (e.g. page 2080, col. 2). The Examiner further stated that Pestronk and applicant's admissions regarding the prior art teach the diagnosis of peripheral neuropathies, including Guillain-Barre syndrome, by determination of autoantibodies directed towards nervous system glycolipid antigens, gangliosides in particular, that Pestronk teaches that GM1, GD1a, GD1b, and GT1b gangliosides are especially abundant in brain and neuronal membranes and that high titers of antibodies to glycolipids, particularly to GM1 gangliosides (Fig. 7), GA 1 ganglioside, and sulfatide, are common in patients with various forms of peripheral neuropathy (cols. 7-10). The Examiner stated that any immunoassay method known to the art may be used to determine antibody levels, including nephelometry (see e.g. col. 16) as a well known form of agglutination assay.

The Examiner stated that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted any conventional particle comprising or coated with surface glycolipids, such as those taught by Dwyer et al., Uemura et al., or Ravindranaths et al., for the liposome particles in the agglutination assays of Uhlig et al. because Dwyer et al. specifically teach the substitution of ganglioside-comprising liposomes with ganglioside-coated polystyrene spheres and one would have had an extremely reasonable expectation that any of the known and conventional particles for agglutination assays, particularly those which were already known to function in agglutination assays involving glycoplipid binding in view of the references, would have performed their expected function of presenting a glycolipid binding ligand to binder and providing a visible indication of the binding interaction. The Examiner stated that it would have been obvious to have provided colored particles for the benefits of increased light contrast taught in Uhlig et al. The Examiner stated that it would have been further obvious to have tested samples from patients with peripheral neuropathies with the method of Uhlig et al., as modified, because, as taught by Pestronk and applicant's admitted prior art, high titers of antibodies to glycolipids are common in patients with various forms of peripheral neuropathy and any assay which functions for detection would have been expected to detect the relevant antibodies as taught by Pestronk. The Examiner stated thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

In response, applicants respectfully traverse the Examiner's rejection. Applicants have hereinabove set forth that none of Uhlig et al., Uemura, or Ravindranaths et al. disclose solid

particles as recited in applicant's claimed invention, and note here that the remaining cited references do not cure this deficiency.

In addition, applicants note that Dwyer et al. does not teach any antibody assay, and there is no suggestion in Dwyer that the system disclosed could be used for anything other than a cholera toxin assay, and no motivation to combine the non-antibody assay teachings with the references teaching antibody assays. Furthermore, applicants note that Dwyer et al. teaches that the monomeric cholera toxin did not agglutinate ganglioside coated latex spheres that the aggregated toxin did (p3232, Materials and Methods, first paragraph), casting doubt on any expectation of successful transference of this system to other assays. The remaining cited references do not cure this deficiency.

Furthermore, contrary to the Examiners assertion regarding Pestronk et al., nephelometry is not a "well known form of agglutination", and in fact is not an assay itself but a broad term (see IUPAC 'Goldbook' definition attached hereto as **Exhibit B**) that is not specific to agglutination assays, and can mean many types of turbidity assay, for example, agglutination inhibition or red cell lysis. Applicants thus maintain that Pestronk does not teach an agglutination assay to determine antibody levels, as claimed by applicants, and the remaining references do not cure this deficiency.

Accordingly, applicants maintain that the rejected claims define an invention not obvious from the cited references, and therefore not properly rejected under 35 U.S.C. 103(a), and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, apart from the total enclosed fee of $253.00, including $43.00 claim fees and a $210.00 fee for a two month extension of time, is deemed necessary in connection with the filing of this Amendment. If any other fee is required, however, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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